$$T_1 = \text{Percent MMT (tetrazole)} = \frac{A_u \times C_s \times P_s \times 100}{A_s \times C_u \times 1{,}000}$$

$$T_2 = \text{Percent related compound} = \frac{R_u \times C_s \times P_s \times 100}{R_s \times C_u \times 1{,}000}$$

$$\text{L} = \text{Percent largest related compound} = \frac{L_u \times C_s \times P_s \times 100}{R_s \times C_u \times 1{,}000}$$

where:

A_u=Area of the tetrazole sample peak;

A_s=Area of the tetrazole working standard peak;

C_s=Concentration of the working standard in milligrams per milliliter;

P_s=Potency of the working standard in micograms per milligram;

C_u=Concentration of the sample solutions in milligrams per milliliter;

R_u=Sum of peak areas of other compounds, excepting MMT and cefpiramide, detected in the sample chromatogram.

R_s=Area of the cefpiramide working standard peak; and

L_u=Area of the largest related peak, except MMT.

T=Percent total related compounds=$T_1 + T_2$.

(5) *Specific rotation.* Dilute an accurately weighed sample with sufficient dimethylformamide to obtain a concentration of approximately 10 milligrams of cefpiramide per milliliter. Proceed as directed in §436.210 of this chapter, using a 1-decimeter polarimeter tube. Calculate the specific rotation on the anhydrous basis.

(6) *Identify.* Proceed as directed in §436.211 of this chapter using a 1-percent potassium bromide disc prepared as directed in §436.211(b)(1).

(7) *Chrystallinity.* Proceed as directed in §436.203(a) of this chapter.

[55 FR 14240, Apr. 17, 1990]

§442.69 Cefmetazole.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Cefmetazole is (6*R*,7*S*)-7-[2-[(cyanomethyl)thio]acetamido]-7-methoxy-3-[[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. It is so purified and dried that:

(i) Its potency is not less than 970 micrograms of cefmetazole activity per milligram.

(ii) Its moisture content is not more than 0.5 percent.

(iii) It gives a positive identity test for cefmetazole.

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, moisture, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research: 10 packages each containing approximately 500 milligrams.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in §442.70a(b)(1).

(2) *Moisture.* Proceed as directed in §436.201 of this chapter.

(3) *Identity.* Proceed as directed in §436.211 of this chapter using a mineral oil mull prepared as described in paragraph (b)(2) of that section.

[59 FR 12546, Mar. 17, 1994]

§442.70a Sterile cefmetazole sodium.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Sterile cefmetazole sodium is the sodium salt of (6*R*-cis)-7-[[[cyanomethyl)thio]acetyl]amino]-7-methoxy-3-[[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. It is a lyophilized powder. It is so purified and dried that:

(i) If the cefmetazole sodium is not packaged for dispensing, its

cefmetazole potency is not less than 860 micrograms and not more than 1,003 micrograms of cefmetazole activity per milligram on an anhydrous basis. If the cefmetazole sodium is packaged for dispensing, its cefmetazole potency is not less than 860 micrograms and not more than 1,003 micrograms of cefmetazole activity per milligram on an anhydrous basis and also, each container contains not less than 90 percent and not more than 120 percent of the number of milligrams of cefmetazole that it is represented to contain.

(ii) It is sterile.

(iii) It contains not more than 0.2 endotoxin units per milligram.

(iv) Its moisture content is not more than 0.5 percent.

(v) The pH of an aqueous solution containing 100 milligrams per milliliter is not less than 4.2 and not more than 6.2.

(vi) It gives a positive identity test.

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for cefmetazole potenty and content (if packaged for dispensing), sterility, bacterial endotoxins, moisture, pH, and identity.

(ii) Samples, if required by the Center for Drug Evaluation and Research:

(A) If the batch is packaged for repacking or for use as an ingredient in the manufacture of another drug:

(*1*) For all tests except sterility: 10 packages, each containing approximately 500 milligrams.

(*2*) For sterility testing: 20 packages, each containing equal portions of approximately 300 milligrams.

(B) If the batch is packaged for dispensing:

(*1*) For all tests except sterility: A minimum of 10 immediate containers of the batch.

(*2*) For sterility testing: 20 immediate containers collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency*. Proceed as directed in §436.216 of this chapter, using ambient temperature, an ultraviolet detection system operating at a wavelength of 214 nanometers, a 25-centimeter X 4.0- or 4.6-millimeter (inside diameter) column packed with microparticulate (5 micrometers in diameter) reversed phase packing material such as octadecyl silane bonded to silicas, a flow rate of not more than 2.0 milliliters per minute, and a known injection volume of between 10 and 20 microliters. Mobile phase, working standard and sample solutions, resolution test solution, system suitability requirements, and calculations are as follows:

(i) *Mobile phase.* Transfer 5.75 grams of ammonium dihydrogen phosphate to a 1-liter container. Add 700 milliliters of deionized water and agitate to aid dissolution. Transfer 3.2 milliliters of 40 percent tetrabutylammonium hydroxide (TBAH) in distilled water to the solution and shake. Add 280 milliliters of methanol and a range 20 to 30 milliliters of tetrahydrofuran and mix well. Adjust the pH to 4.5±0.1 with phosphoric acid. The mobile phase is 0.05*M* ammonium dihydrogen phosphate: methanol: tetrahydrofuran (700:280:20–30). It is 0.005*M* with respect to TBAH. Filter the mobile phase through a suitable filter capable of removing particulate matter to 0.5 micron in diameter and degas it just prior to its introduction into the chromatograph.

(ii) *Preparation of working standard, sample, and resolution test solutions*—(A) *Working standard solution.* Dissolve and dilute and accurately weighed portion of the cefmetazole working standard in sufficient mobile phase to obtain a solution containing 0.2 milligram of cefmetazole activity per milliliter. Analyze this solution within 10 minutes.

(B) *Sample solutions*—(*1*) *Product not packaged for dispensing (micrograms of cefmetazole per milligram).* Dissolve an accurately weighed sample with sufficient mobile phase to obtain a solution containing approximately 0.2 milligram of cefmetazole per milliliter (estimated). Analyze this solution within 10 minutes.

(*2*) *Product packaged for dispensing.* Determine both micrograms of cefmetazole per milligram of sample and milligrams of cefmetazole per container. Use separate containers for

preparation of each sample solution as described in paragraphs (b)(1)(ii)(B)(*2*)(*i*) and (*ii*) of this section.

(*i*) Micrograms *of cefmetazole per milligram.* Dissolve an accurately weighed sample with sufficient mobile phase to obtain a solution containing approximately 0.2 milligram of cefmetazole per milliliter (estimated). Analyze this solution within 10 minutes.

(*ii*) *Milligrams of cefmetazole per container.* Reconstitute the sample as directed in the labeling. Then, using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute the solution thus obtained with sufficient distilled water to obtain a solution containing 1,000 micrograms of cefmetazole activity per milliliter (estimated). Further dilute this solution with mobile phase to obtain a solution containing 0.2 milligram of cefmetazole activity per milliliter (estimated). Analyze this solution within 10 minutes.

(C) *Resolution test solution.* Dissolve an accurately weighed portion of cefmetazole working standard in 0.01*N* sodium hydroxide to obtain a solution containing approximately 1.0 milligram of cefmetazole activity per milliliter. Heat this solution at 95 °C for 10 minutes. This procedure generates cefmetazole lactone. Dilute 1.0 milliliter of this solution to 20 milliliters with mobile phase.

(iii) *System suitability requirements*—(A) *Asymmetry factor.* Calculate the asymmetry factor (A_s), measured at a point 10 percent of the peak height from the baseline as follows:

$$A_s = \frac{a+b}{2a}$$

where:

a=Horizontal distance from point of ascent to point of maximum peak height; and
b=Horizontal distance from point of maximum peak height to point of descent.

The asymmetry factor (A_s) is satisfactory if it is not less than 0.94 and not more than 1.6.

(B) *Efficiency of the column.* From the number of theoretical plates (*n*) calculated as described in § 436.216(*c*)(2) of this chapter calculate the reduced plate height (h_r) as follows:

$$h_r = \frac{(L)(10{,}000)}{(n)(d_p)}$$

where:

L = Length of the column in centimeters;
n = Number of theoretical plates; and
d_p = Average diameter of the particles in the analytical column packing in micrometers.

The absolute efficiency (h_r) is satisfactory if it is not more than 20 for the cefmetazole peak.

(C) *Resolution factor.* The resolution factor (*R*) between the peak for cefmetazole and the peak for cefmetazole lactone (generated in situ) is satisfactory if it is not less than 3.0.

(D) *Coefficient of variation (relative standard deviation).* The coefficient of variation (S_R in percent of 5 replicate injections) is satisfactory if it is not more than 2.0 percent.

(E) *Capacity factor (k′).* Calculate the capacity factor (*k′*) for cefmetazole as follows:

$$k' = \frac{t_r - t_o}{t_o}$$

where:

t_r=Retention time of cefmetazole in minutes; and
t_o=Column dead time in minutes, which is estimated from the following equation:

$$t_o = \frac{(3.1416)(D^2)(L)(0.75)}{4F}$$

where:

D=Column diameter in centimeters;
L=Column length in centimeters;
0.75=Average total column porosity; and
F=Flow rate in milliliters per minute.

The capacity factor (*k′*) for cefmetazole is satisfactory if it is not less than 2.0 and not more than 8.0. If the system suitability parameters have been met, then proceed as described in § 436.216(b) of this chapter.

(iv) *Calculations*—(A) *Cefmetazole potency (micrograms of cefmetazole per milligram).* Calculate the micrograms of

cefmetazole per milligram of sample as follows:

$$\text{Micrograms of cefmetazole per milligram} = \frac{A_u \times P_s \times 100}{A_s \times C_u \times (100 - m)}$$

where:

A_u=Area of the cefmetazole peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

A_s=Area of the cefmetazole peak in the chromatogram of the cefmetazole working standard;

P_s=Cefmetazole activity in the cefmetazole working standard solution in micrograms per milliliter;

C_u=Milligrams of cefmetazole sample per milliliter of sample solution; and

m=Percent moisture content of the sample.

(B) *Cefmetazole content (milligrams of cefmetazole per container).* Calculate the cefmetazole content of the container as follows:

$$\text{Milligrams of cefmetazole per container} = \frac{A_u \times P_s \times d}{A_s \times 1{,}000}$$

where:

A_u=Area of the cefmetazole peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

A_s=Area of the cefmetazole peak in the chromatogram of the cefmetazole working standard;

P_s=Cefmetazole activity in the cefmetazole working standard solution in micrograms per milliliter; and

d=Dilution factor of the sample.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in § 436.20(e)(1).

(3) *Bacterial endotoxins.* Proceed as directed in the United States Pharmacopeia bacterial endotoxins test.

(4) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(5) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 100 milligrams per milliliter.

(6) *Identity.* Proceed as directed in § 436.211 of this chapter using a mineral oil mull prepared as described in § 436.211(b)(2).

[55 FR 6634, Feb. 26, 1990]

§ 442.80 Cefprozil.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Cefprozil is an approximate 9:1 mixture of the Z (cis) and the E (trans) isomers, respectively, of (6*R*,7*R*)-7-[(*R*)-2-amino-2-(*p*-hydroxyphenyl)acetamido]8-oxo-3-propenyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. It is so purified and dried that:

(i) Its potency is not less than 900 micrograms nor more than 1,050 micrograms of cefprozil activity per milligram, on an anhydrous basis.

(ii) The ratio of its (E) isomer to total cefprozil is not less than 0.06 nor more than 0.11.

(iii) Its moisture content is not less than 3.5 percent nor more than 6.5 percent.

(iv) The pH of an aqueous solution containing 5 milligrams per milliliter is not less than 3.5 nor more than 6.5.

(v) It is crystalline.

(vi) It gives positive identity tests.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for cefprozil potency, E isomer to total cefprozil ratio, moisture, pH, crystallinity, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research: 10 packages, each containing approximately 500 milligrams.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 436.216 of this chapter, using ambient temperature, an ultraviolet detection system operating at a wavelength of 280 nanometers, a 25 centimeter × 3.9 to 4.6 millimeter (id) column packed with microparticulate (5 to 10 micrometers in diameter) reversed phase packing material such as octadecyl silane bonded to silicas, a flow rate of 1.0 milliliter per minute, and a known injection volume of 10 microliters. The retention time for cefprozil (Z) is between 4 and 6 minutes and the retention time for cefprozil (E) is between 6 and 8 minutes. Mobile phase, working standard